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~~X, which may or may not be present, is a substituted or unsubstituted alkyl group;
P is an organic or inorganic polymer; and
M is at least one nucleotide.~~

REMARKS

The undersigned takes this opportunity to thank Examiner Crane for the courteous telephone interview of May 28, 1999, during which he agreed to consider this Supplemental Amendment. The prosecution of this application was recently transferred to the undersigned Representatives for Applicants, Pennie & Edmonds LLP, and this Supplemental Amendment is being filed to better clarify that which Applicants regard as the invention.

Claims 48-79 are currently pending in this application for the Examiner's review and consideration. The Reply and Amendment under 37 C.F.R. § 1.111 filed on February 5, 1999 canceled claims 18-31 and added claims 32-47. Claims 32-47 are canceled above. New claims 48-62 recite solid supports of the invention; new claims 63-75 recite specific solid supports of the invention; and new claims 76-79 recite solid supports of the invention coupled to at least one nucleotide.

All of new claims 48-79 are fully supported by the specification as filed, and no new matter has been introduced. To be specific, support for claims 48-62 can be found in the specification at, for example, page 6, line 30 - page 8, line 1 and page 10, line 1 - page 11, line 6. As suggested by the Examiner on page 4 of the Office Action, claim 48, like claims 63-65 and 76-79, recites a chemical formula to make the scope and nature of the invention more clear.

Support for claims 63-75 can be found in the specification at, for example, page 10, line 1 - page 11, line 6. Support for claims 76-79 can be found, for example, in the specification at page 14, lines 1 - 5 and Scheme 2, page 20.

Rejections Under 35 U.S.C. §112, Second Paragraph

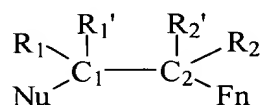
As set forth on pages 2-5 of the Office Action, claims 18-31 were rejected under the second paragraph of 35 U.S.C. §112 as allegedly failing to particularly point out and distinctly claim the invention. These rejections have been obviated or are traversed for the reasons provided below.

On page 2 of the Office Action, claims 18, 23, 26, 27, and 28 are rejected for their use of the terms "comprising" and "including." Although these claims have been canceled, this rejection is respectfully traversed for the reasons provided below to the extent it may be applied to new claims 48, 63-65, and 76-79, all of which use the term "comprising."

This invention is based in part on the unexpected discovery that certain chemical moieties having specific reactivities, positioned on adjacent carbon atoms, and coupled directly or indirectly to polymers allow the efficient, universal synthesis of polynucleotides. *See, e.g.*, specification, page 5, lines 19-31. Upon completion of polynucleotide synthesis, this unique combination of chemical moieties further allows the one-step cleavage of a hydroxyl-terminated polynucleotide from the support. The invention is thus not limited to specific compounds, but instead encompasses any compound that contains the specific arrangements of moieties taught by the instant application. It is therefore respectfully submitted that the term “comprising” used in claims 48, 63-65, and 76-79 is necessary to recite the true scope of the invention, and does not render these claims indefinite.

On page 3 of the Office Action, claim 18 is rejected for its use of functional language, and detailed suggestions are made on pages 4-5 of the Office Action concerning the use of functional language. Independent claims 48, 63-65, and 76-79 recite chemical structures in view of these suggestions. The solid supports recited by new claims 48 and 76 are, however, defined to some extent by the chemical reactivities of moieties they comprise. To the extent that these definitions are considered by the Examiner to be functional language, a rejection of claim 48 or 76 for the use of such language is respectfully traversed.

Claim 48 recites a universal solid support for the solid phase synthesis of polynucleotides. This solid support comprises an organic or inorganic polymer coupled to a compound of the formula:



As discussed above, the invention does *not* depend upon the precise structures of the moieties (*i.e.*, R_1 , R_1' , R_2 , R_2' , Nu, and Fn) bound to the first (C_1) and second (C_2) carbon atoms. The invention *is*, however, limited by the reactivities of each of these groups. For example, the oxygen atom of the Fn moiety must be capable of bonding to the 3' or 5' phosphate, phosphite, or phosphorothioate group of a nucleotide under conditions the same as those used for polynucleotide synthesis. Similarly, the nucleophile bound to C_1 must be capable of cleaving the 3' or 5' phosphate, phosphite, or phosphorothioate group from a nucleotide bound to the oxygen atom of Fn under *different* reaction conditions. Because the reactivities of individual chemical moieties are well known to those skilled in the art, *see, e.g.*, J. March, *Advanced Organic Chemistry*, Appendix B, pp. 1269-1300 (4th ed., 1992) (a copy of which is attached hereto as Exhibit A), it is respectfully submitted that the metes and bounds of claims 48 and 76 are well defined.

On page 3 of the Office Action, claim 18 is rejected for its use of the phrase “inert groups ...” This rejection has been obviated by incorporating the language suggested by the Examiner into new claims 48, 63-65, and 76-79.

Also on page 3 of the Office Action, claims 19 and 29 are rejected as unclear. These claims have been canceled. The subject matter of claims 19 and 29 is now more clearly recited by claims 59 and 71, respectively.

On pages 3-4 of the Office Action, claims 20 and 28 are rejected as unclear for their use of the term “moiety.” This rejection has been obviated by, for example, the simple recitation in claim 48 that R_1' and R_2' can be taken together to form a ring coupled to the organic or inorganic polymer. Because the ring itself can include any group of atoms inert to solid phase reaction conditions, the recitation of “an unsubstituted or substituted moiety” is unnecessary.

On page 4 of the Office Action, claims 21 and 22 are rejected as providing conflicting perspectives on the nature of the nucleophile. This rejection has been overcome by canceling claims 21 and 22 and adding new claims 60 and 61. As claim 61 makes clear, it is the moiety containing both the nucleophile and the protecting group that has the structure $-OC(O)CH_3$. The Examiner's attention is further directed to claims 71 and 72.

Also on page 4 of the Office Action, claim 24 is rejected as reciting broad functional language. Although it appears that the Examiner was instead referring to claim 23, this rejection has been obviated by the cancellation of both claims 23 and 24. The subject matter recited by claims 23 and 24 is now more clearly recited by new claim 48, the language of which is discussed more fully above.

The rejection of claims 21, 22, 30, and 31 set forth on page 4 of the Office Action has also been overcome. The subject matter of these claims is now more clearly recited by new claims 60, 61, 71, and 72.

Finally, the rejection of claims 24 and 25 set forth on page 4 of the Office Action has been overcome. Claims 24 and 25 have been canceled and new claims 50, 67, and 69 have been added. These new claims make clear that “acyl” rather than “acetyl” moieties are contemplated.

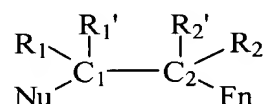
Rejections Under 35 U.S.C. §102

As set forth on pages 5-6 of the Office Action, claims 18-20 and 23-27 are rejected under 35 U.S.C. §102(a) and (b). To the extent these rejections may be applied to new claims 48-79, they are respectfully traversed for the following reasons.

On pages 5-6 of the Office Action, claims 18-20 and 23-27 are rejected under §102(a) as allegedly anticipated by Lyttle *et al.*, *Nucleic Acids Res.* 24(14):2793-2798 (1996) (“Lyttle”). On page 6 of the Office Action, claims 18-20 and 23-27 are rejected under §102(b) as allegedly anticipated by Vu *et al.*, *Bioconjugate Chemistry* 5(5):599-606 (1995) (“Vu”). Both rejections are traversed as being published after the priority date of the application (July 9, 1993). Applicants respectfully remind the Examiner that he acknowledged the unavailability of both Lyttle and Vu as prior art during the prosecution of parent application no. 08/591,466 in the Interview Summary dated October 2, 1997 (paper no. 8).

On page 6 of the Office Action, claims 18-20 and 23-27 are rejected under §102(b) as allegedly anticipated by U.S. Patent No. 4,659,774 to Webb *et al.* (“Webb”). Webb discloses a support for oligonucleotide synthesis of the formula P'-S', wherein P' is a polymer support and S' is a long chain alkylamine spacer of the formula W-(CH₂)_a-X-(CH₂)_b-Y-(CH₂)_c-Z, each of W and Z independently comprises a nucleophile, X and Y, which may or may not be present, comprise groups of high hydrophilicity, and a, b, and c are integers from zero to nine where b + c is greater than six. Col. 1, line 55 - col. 2, line 5; col. 4.

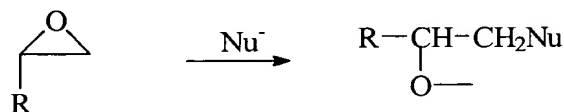
Unlike Webb, the solid support recited by claim 48 comprises an organic or inorganic polymer coupled to a compound of the formula:



wherein the Nu and Fn moieties are specifically defined in terms of their reactivities.

Because these groups are positioned on adjacent carbon atoms, instead of on carbon atoms separated by at least five other carbon atoms, claim 48 is clearly not anticipated by the solid support disclosed by Webb.

Webb further discloses a method of preparing supports for oligonucleotide synthesis, *one step* of which is based on the general reaction:



wherein R is either undefined or is hydrogen, alkyl, or aryl. Col. 2, lines 51-65; col. 3, line 17. This disclosure fails to anticipate the invention as currently claimed for several reasons. First, even assuming that R is defined, the product of the reaction is not bound to a solid

support. At most, the reaction product simply represents an intermediate used by Webb in the preparation of a solid support.

Second, Webb fails to even suggest that the moiety represented by Nu in the formula of the reaction product is a nucleophile, much less one having the chemical reactivity recited by, for example, new claim 48. This is because Webb only teaches that the *anion* of Nu (*i.e.*, Nu⁻) is a nucleophile. Col. 2, line 53. Webb further teaches that Nu⁻ is only capable of cleaving an oxirane in neutral or basic solutions. Col. 2, lines 52-56. Webb thus neither discloses nor suggests a nucleophile bound adjacent to an unprotected or protected hydroxyl group that is capable of cleaving a 3' or 5' phosphate, phosphite, or phosphorothioate group from a nucleotide.

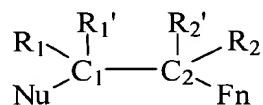
Third, because Webb provides little or no information concerning the chemical reactivity or steric bulk of the R and Nu moieties of the reaction product shown above, it fails to even suggest an unprotected oxygen atom that can form a covalent bond with the 3' or 5' phosphate, phosphite, or phosphorothioate group of a nucleotide under conditions that are the same as those used for polynucleotide synthesis. Consequently, and in view of the facts provided above, Applicants respectfully submit that Webb fails to anticipate or render obvious the universal solid support recited by new claims 48-62.

Applicants further point out that Webb fails to anticipate or render obvious any of claims 63-79. For example, both the nucleophile and the organic or inorganic polymer are bound directly or indirectly to the same carbon atom (*i.e.*, C₁) in the structure recited by claim 65. By contrast, the polymer and nucleophile are bound to different carbon atoms in the general structure disclosed by Webb. For these reasons, it is respectfully submitted that the rejection of claims 18-20 and 23-27 as anticipated by Webb cannot be applied to the invention as currently recited by any of claims 48-79.

On page 6 of the Office Action, claims 18-20 are rejected under §102(b) as allegedly anticipated by Nelson *et al.*, *Nucleic Acids Research* 17(18):7187-7194 (1989) ("Nelson"). Nelson discloses a pore glass "which introduces an aliphatic primary amine to the 3' terminus of an oligonucleotide via solid phase synthesis." Nelson, p. 7187, final paragraph. The structure of the pore glass is disclosed in Figure 1 on page 7188.

Unlike the support disclosed by Nelson, universal solid supports of this invention do *not* introduce foreign moieties onto the 3' terminus of a polynucleotide. This is one of the advantages of the claimed invention. *See, e.g.*, specification, p. 6, lines 15-22. Also unlike the support disclosed by Nelson, supports of the claimed invention are capable of binding to the 3' or the 5' phosphate, phosphite, or phosphorothioate group of a nucleotide. *See, e.g.*,

specification, p. 6, lines 30-39. This particular advantage of the invention is made clear by claim 48, which recites a solid support comprising a compound of formula:



wherein Fn comprises an oxygen atom capable of bonding to the 3' or 5' phosphate, phosphite, or phosphorothioate group of a nucleotide under the same set of reaction conditions used for the polynucleotide synthesis. Finally, Nelson does not disclose or suggest a nucleophile capable of cleaving the 3' or 5' phosphate, phosphite, or phosphorothioate group from a nucleotide bound to C₁ via an oxygen atom. For these reasons, Applicants respectfully submit that Nelson neither anticipates nor renders obvious the invention as now recited by claims 48-62.

Applicants further submit that Nelson fails to anticipate or render obvious the invention as recited by claims 62-79. First, Nelson does not disclose or suggest cyclic structures such as those recited by claims 62, 63, 76, and 77. Second, Nelson does not disclose a compound such as that recited by claim 65, wherein a nucleophile is attached to the same carbon atom (*i.e.*, C₁) to which the inorganic or organic polymer is attached.

Rejections Under 35 U.S.C. §103(a)

As set forth on pages 6-7 of the Office Action, claims 21, 22, and 28-31 are rejected under 35 U.S.C. §103(a) over U.S. Patent No. 5,362,866 to Arnold ("Arnold"). To the extent these rejections may be applied to new claims 48-79, they are respectfully traversed.

Arnold discloses compounds of the formulas:



wherein S is a solid support, R₇ and R₈ are protecting groups, and R₉ is H, alkyl, alkoxy, or aryl. *See, e.g.*, col. 19, line 13 - col. 20, line 3. In the process disclosed by Arnold, the protecting group R₇ is removed and the oxygen atom to which it was bound is attached to an oligonucleotide. The adjacent oxygen atoms, initially protected by R₈, are then oxidized and the bond between them cleaved. *See, e.g.*, Figures 1a, 2a, and 3; col. 7, lines 36-43; and claim 1, col. 18, line 56 - col. 19, line 12. When a compound disclosed by Arnold is used for

the synthesis of an oligonucleotide, the final oligonucleotide product is cleaved from the compound using an oxidant. *See, e.g.*, col. 9, lines 5-11; and Example 4, col. 13, line 42 - col. 14, line 37. The cleaved oligonucleotide product contains a terminal phosphate, phosphite, or phosphorothioate group. *See, e.g.*, Figure 1a.


From the above, it is clear that Arnold neither teaches nor suggests the solid supports of this invention. First, the solid supports of this invention comprise a functional group Fn positioned β to an unprotected or protected nucleophile Nu. Arnold does not suggest such an α - β arrangement. Second, Arnold provides no suggestion that the oxygen atom of Fn can bond to the 3' or 5' phosphate, phosphite, or phosphorothioate group of a nucleotide under the same reaction conditions used to synthesize a polynucleotide. And third, the nucleophile of this invention is capable of cleaving the 3' or 5' phosphate, phosphite, or phosphorothioate group from a nucleotide bound to the oxygen atom of Fn and in so doing yield a *hydroxyl-terminated polynucleotide*. Arnold teaches away from such a nucleophile by focusing exclusively on the use of oxidants to cleave the final product, which contains a terminal phosphate, phosphite, or phosphorothioate group, from the solid support. *See, e.g.*, col. 9, lines 5-11; Example 4, col. 13, line 42 - col. 14, line 37; and Figure 1a. In view of these differences, Applicants respectfully submit that the present invention as recited by claims 48-79 is not obvious over Arnold either alone or in view of the other cited references.

Conclusion

In conclusion, it is believed that new claims 48-79 recite the invention in a clear and definite manner. It is further believed that none of the references cited by the Examiner anticipates or renders obvious the invention as claimed. Applicants thus respectfully submit that each ground for rejection has been successfully obviated and that the application is in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application is earnestly requested.

Respectfully submitted,

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Enclosures